45 44
109. The composition of claim 108, wherein said IGF-I is present in said composition at a concentration of about 15 mg/ml to about 200 mg/ml.

46 45
110. The composition of claim 109, wherein said IGF-I is present in said composition at a concentration of about 25 mg/ml to about 200 mg/ml.

C1

47 37
111. The composition of claim 101, wherein said composition comprises sodium chloride at a molar concentration of about 150 mM.

48 37
112. The composition of claim 101 comprising a buffer selected from the group consisting of a glutaric acid buffer, a maleic acid buffer, a succinic acid buffer, a citric acid buffer, imidazole, and a histidine buffer.--

REMARKS

Claims 49-84 have been canceled subject to the restriction requirement. Applicants expressly reserve the right to file divisional applications or take such other appropriate measures deemed necessary to protect the inventions in these claims. New claims 85-112 have been added. Support for the new claims resides throughout the specification and in the original claims. No new matter is added by way of presentation of new claims. Claims 29-48 and 85-112 are pending in the application. Reexamination and reconsideration of the claims is respectfully requested.

The Examiner's remarks in the Office Action are addressed below in the order set forth therein.

The Rejection of the Claims under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 29-48 are rejected under 35 U.S.C. 103(a) as being obvious in view of Chang *et al.*, U.S. Patent No. 5,410,026. This rejection is respectfully traversed.

Chang *et al.* teach a method for refolding insoluble, misfolded IGF-I that has precipitated as refractile bodies within a prokaryotic host cell. The method comprises isolating the refractile bodies from the host cell, and then incubating the refractile bodies in alkaline buffer containing the minimum amount of a chaotropic agent and of a reducing agent necessary to solubilize the misfolded IGF-I and to allow for its unfolding and refolding. The reference teaches urea and guanidine hydrochloride as chaotropic agents, where urea is at a concentration of about 1.5-2.5M, and guanidine hydrochloride is at a concentration of about 1-3 M. See column 10, lines 39-42. The reference demonstrates that in the absence of the reducing agent, resolubilization of the misfolded IGF-I does not occur. See column 18, lines 16-19 and Table 1. The fact that a reducing agent must be present is an indication that the misfolded IGF-I in these refractile bodies exists as a conglomeration of IGF-I molecules that have mismatched or unformed disulfide bonds. See the Chang reference at column 8, lines 1-20.

The method disclosed by the Chang *et al.* reference teaches that yield of correctly folded IGF-I from refractile bodies is dependent upon initial concentration of the insoluble IGF-I added to the refolding buffer solution. The preferred concentration of insoluble IGF-I within the refolding buffer solution at the start of the incubation period is in the range of 0.5-5.5 mg/ml (approximately 0.06 mM to 0.72 mM), more preferably 1.5-5.0 mg/ml (approximately 0.2 mM to 0.7 mM). See column 11, lines 1-3, column 20, lines 1-6. When higher concentrations of insoluble IGF-I are added to the refolding buffer solution, the yield of correctly folded protein declines. See Figure 12. When viewed as a composition, the starting material disclosed in this reference is a buffered solution having 0.5-5.5 mg/ml of misfolded IGF-I. Thus, following incubation, this composition would contain at most 5.5 mg/ml IGF-I in a soluble form if all of the insoluble IGF-I were to become solubilized following the incubation period; of this, only a fraction is correctly folded IGF-I. The reference does not disclose a composition having a pH of

at least 5.5 that comprises a high concentration of biologically active IGF-I (at least about 12 mg/ml) that remains soluble in the composition, even when the composition is stored at a temperature of about 4°C. The method disclosed in the Chang *et al.* patent does not use, or suggest the use of, guanidine hydrochloride as a solubilizing agent in the manner recited in Applicants' claimed compositions.

Furthermore, the method disclosed in the Chang *et al.* reference uses an incubation temperature of generally 10°C-40°C, more preferably 20°C-40°C. Example II B, which uses urea as the chaotropic agent, clearly demonstrates that recovery of correctly folded IGF-I is reduced by 50% when the method is carried out at 4°C. See column 20, lines 10-13 and Tables 4 and 5. The reference does not teach or suggest Applicants' discovery that a solubilizing compound comprising a guanidinium group, in the concentration range disclosed in the specification, increases solubility of biologically active IGF-I in a composition, even when that composition is stored at 4°C.

Claims under prosecution in the present application are directed to compositions comprising biologically active IGF-I, or biologically active analogue thereof, and a solubilizing compound in an amount sufficient to make the IGF-I or analogue thereof soluble at a concentration of at least about 12 mg/ml when the composition is at a temperature of about 4°C. The solubilizing compound comprises a guanidinium group. Specific solubilizing compounds recited in the claims include guanidine hydrochloride, arginine, or an arginine analogue. Applicants respectfully submit that these compositions are not taught by, nor rendered obvious by, the cited reference. The compositions of the Chang *et al.* reference comprise at most 5.5 mg/ml IGF-I, which starts out as insoluble misfolded protein. Further, Figure 12 demonstrates that the amount of correctly folded protein recovered declines as insoluble IGF-I concentration in the starting material exceeds about 0.7 mM, or about 5.0 mg/ml. The reference specifically teaches away from using higher concentrations of IGF-I in the starting material, and thus teaches away from the use of a solubilizing agent comprising a guanidinium group, such as guanidinium hydrochloride, to prepare the compositions of the present invention.

As the cited reference does not teach or render obvious the claimed invention, Applicants respectfully submit that the rejection should be withdrawn.

New Claims Added

New claims 85-112 have been added. These claims are directed to specific embodiments of the pending claims. Thus, the newly recited compositions comprise human IGF-I and a solubilizing agent having a guanidinium group (claims 85-100) or arginine (claims 101-112) in an amount sufficient to make the IGF-I soluble at a concentration of at least about 12 mg/ml when the composition is at a temperature of about 4°C. Applicants respectfully submit that these compositions are not taught or rendered obvious by the cited reference.

Consideration of Previously Submitted Information Disclosure Statement

It is noted that an initialed copy of the PTO Form 1449 that was submitted with Applicants' Information Disclosure Statement filed April 16, 1999, and the PTO Form 1449 that was submitted with Applicants' Supplemental Information Disclosure Statement filed May 19, 1999, have not been returned to Applicants' representative with the Office Action. Accordingly, it is requested that an initialed copy of the Form 1449 for each of these statements be forwarded to the undersigned with the next communication from the PTO. In order to facilitate review of the references by the Examiner, a copy of the Information Disclosure Statements and their Form 1449 are attached hereto. Copies of the cited references were provided at the time of filling the original Information Disclosure Statement, and, therefore, no additional copies of the references are submitted herewith. Applicants will be pleased to provide additional copies of the references upon the Examiner's request if it proves difficult to locate the original references.

CONCLUSION

In view of the above remarks, Applicants submit that the rejection of the claims under 35 U.S.C. §103(a) is overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Version with Markings to Show Changes Made:

In the Claims:

Please cancel claims 49-84 without prejudice to or disclaimer of the subject matter encompassed thereby.